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EXPEDITED REVIEW

Reduction of Morbidity and Mortality by Statins, Angiotensin-Converting Enzyme Inhibitors, and Angiotensin Receptor Blockers in Patients With Chronic Obstructive Pulmonary Disease

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OBJECTIVES The purpose of this study was to determine if statins (hydroxymethylglutaryl CoA reductase inhibitors [HMG-CoA]), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) reduce cardiovascular (CV) events and pulmonary morbidity in chronic obstructive pulmonary disease (COPD) patients.

BACKGROUND Few current COPD therapies alter prognosis. Although statins, ACE inhibitors, and ARBs improve outcomes in CV populations, their benefits in COPD patients both with and without concomitant heart disease has not previously been studied.

METHODS A time-matched nested case-control study of two population-based retrospective cohorts was undertaken: 1) COPD patients having undergone coronary revascularization (high CV risk cohort); and 2) COPD patients without previous myocardial infarction (MI) and newly treated with nonsteroidal anti-inflammatory drugs (low CV risk cohort). Prespecified outcomes were COPD hospitalization, MI, and total mortality.

RESULTS These drugs reduced both CV and pulmonary outcomes, with the largest benefits occurring with the combination of statins and either ACE inhibitors or ARBs. This combination was associated with a reduction in COPD hospitalization (risk ratio [RR] 0.66, 95% confidence interval [CI] 0.51 to 0.85) and total mortality (RR 0.42, 95% CI 0.33 to 0.52) not only in the high CV risk cohort but also in the low CV risk cohort (RR 0.77, 95% CI 0.67 to 0.87, and RR 0.36, 95% CI 0.28 to 0.45, respectively). The combination also reduced MI in the high CV risk cohort (RR 0.39, 95% CI 0.31 to 0.49). Benefits were similar when steroid users were included.

CONCLUSIONS These agents may have dual cardiopulmonary protective properties, thereby substantially altering prognosis of patients with COPD. These findings need confirmation in randomized clinical trials. (J Am Coll Cardiol 2006;47:2554–60) © 2006 by the American College of Cardiology Foundation

Chronic obstructive pulmonary disease (COPD) is increasing in prevalence, leading to escalating hospitalization and mortality risks. Apart from smoking cessation in all patient groups and oxygen in severely affected patients, there is controversy as to whether therapies used in routine practice modify outcome (1–3). Cardiovascular (CV) events are increasingly being recognized as a major cause of death in patients with diverse forms of lung disease (4–10). We hypothesized that medications currently associated with CV risk reduction might have a substantial impact on the clinical outcome of COPD patients by at least reducing the CV component of adverse morbidity and mortality in these patients. In addition, we hypothesized that statins (hydroxymethylglutaryl CoA reductase inhibitors [HMG-CoA]) and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), through pleiotropic mechanisms, might also modify outcomes directly attributed to lung disease itself (11). The latter conjecture is based on mechanistic studies showing the potential importance of these drugs in mitigating diverse forms of lung injury (12–24). Accordingly, we used population databases to explore the impact of these drugs on the outcome of patients with COPD with respect to both pulmonary and CV events as well as to overall mortality. The purpose of this study was to determine whether there is evidence suggesting dual cardiopulmonary protective properties of these agents and to provide a rationale for undertaking more definitive randomized clinical trials.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
CI = confidence interval
COPD = chronic obstructive pulmonary disease
CV = cardiovascular
HMG-CoA = hydroxymethylglutaryl CoA reductase inhibitors
MI = myocardial infarction
NSAID = nonsteroidal anti-inflammatory drug
RR = risk ratio

METHODS

Using the Quebec Linked Databases, we conducted a retrospective cohort study which was analyzed using a time-matched nested case-control approach to assess the association between CV drug use (statins, ACE inhibitors, and ARBs) and the risk of hospitalization secondary to COPD, myocardial infarction (MI), and death. These administrative databases have been developed for the universal health care programs for Quebec citizens. They capture all physician visits, procedures, hospitalizations, and outpatient prescription drugs (quantity, strength, dosage, and date of dispensing). The hospital database captures information on all patient demographics, admission and discharge dates, procedures, and up to 15 secondary diagnoses. These databases have been previously validated and extensively used in research (25,26). A nested case-control approach was used because the whole cohort was too large to analyze using a survival analysis model with time-dependent covariates (exposure to the medications of interest).

Cohort entry. We tested our hypothesis among two distinct COPD cohorts, because the magnitude of the benefit for statins, ACE inhibitors, and ARBs may differ among those with different CV risk profiles: 1) a cohort of revascularized patients with relatively high CV risk profile; and 2) a general population cohort of nonsteroidal anti-inflammatory drug (NSAID) users without previous MI.

The source population for the first cohort consisted of elderly (65 years or older) revascularized (percutaneous coronary angioplasty and/or bypass grafting) patients (25). In brief, patients with the first revascularization procedure during the period April 1, 1995, to December 31, 2000, were followed until December 31, 2002. Patients may have had previous revascularization procedures before April 1, 1995. Patients were excluded from the cohort if they were <65 years of age at the time of their revascularization procedure, were non-Quebec residents, or died in the hospital during their initial revascularization. (25).

The source population for the second cohort with a lower CV risk profile was also analyzed and consisted of a random sample of residents of Quebec (65 years or older) who received a prescription for an NSAID between January 1, 1999, and June 30, 2002 (26), and again were followed until December 31, 2002. This second cohort specifically excluded any patient with an MI in the five years preceding cohort entry.

From each of these two source populations we identified subcohorts of COPD subjects who were prescribed at least three prescriptions on two different dates within the preceding year for a beta$_2$-agonist, inhaled anticholinergic, or theophylline (27). The date of the third prescription was chosen as the date of entry into each of the COPD study cohorts. Those who had used at least one prescription of an inhaled steroid, nasal steroid, and other drugs including nedocromil, ketotifen, and cromoglycate during the year preceding cohort entry were excluded to avoid inclusion of subjects who had a primary diagnosis of asthma. However, we also examined COPD cohorts allowing those who used oral or inhaled steroids but not nasal steroids, because the latter group most likely represented patients with allergic conditions. This analysis is important, because there is controversy as to the impact of steroid use on outcome of COPD patients (3).

Members of both COPD cohorts were followed to: 1) the first occurrence of our predefined study end points (hospitalization for COPD, MI, or death); 2) the emigration from the province; or 3) the end of study period. All hospitalizations secondary to COPD (ICD-9 codes 490 to 492 and 496) as well as hospital admissions due to acute MI (ICD-9 code 410) were identified using the primary discharge diagnosis code. The date of first hospitalization for COPD or MI was designated as the index date. The analysis of these end points employed a nested case-control methodology. The advantages of this analytical technique in assessing CV outcomes have been previously described (28). Basically, for each case of each end point, a risk set of all potential controls consisting of all cohort members with the same age (±1 year) and year of cohort entry as the case and still at risk of the event was formed. This ensured equal follow-up time for cases and controls. From this risk set, 20 controls were randomly selected and assigned the diagnosis date of the matched case. Statin, ARB, and ACE inhibitor users were defined as currently exposed if they received at least one prescription in the 60 days before the index date. Past users were those who received the drugs of interest more remotely than 60 days. In addition to our interest in single agents, we were interested in the effect of combination therapy, defined as statin use plus either an ACE inhibitor or an ARB. Drugs other than statins, ACE inhibitors, and ARBs were treated as covariates.

Statistical analysis. Using conditional logistic regression, unadjusted risk ratios (RRs) were computed comparing the risks in the exposed groups taking statins, ACE inhibitors, and/or ARBs to a reference group of those not taking any of the three drugs. Adjusted RRs were calculated controlling for potential confounders identified using both the hospitalization records and from the pharmaceutical database. Specifically, we adjusted for the effects of gender, age, history of prior hospitalization for MI, congestive heart failure, or pneumonia, number of drugs used at entry,

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Table 1. Summary of Number of Cases and Controls for Each End Point Examined in the High- and Low-Risk Cohorts

Cohort	End Point	Steroid Users	Cases (n)	Controls (n)
High-risk	Hospitalization for COPD	Excluded	946	18,774
		Included	1,028	20,429
	MI	Excluded	1,028	20,385
		Included	1,111	22,064
	Death	Excluded	1,009	20,011
		Included	1,092	21,692
	Death or MI	Excluded	2,058	40,829
		Included	2,226	44,227
Low-risk	Hospitalization for COPD	Excluded	4,907	98,097
		Included	5,344	106,852
	MI	Excluded	491	9,820
		Included	529	10,580
	Death	Excluded	2,219	44,260
		Included	2,368	47,240
	Death or MI	Excluded	2,710	54,080
		Included	2,897	57,820

COPD = chronic obstructive pulmonary disease; MI = myocardial infarction.

number of physician visits before entry, use of inhaled anticholinergics, steroids, and beta$_2$-agonists, theophylline, beta-blockers, calcium-channel blockers, diuretics, nitrates, and diabetes therapies. It should be noted that the databases do not allow for assessment of COPD severity based on lung function testing, biochemical severity of dyslipidemia, smoking status/quantity, or severity of hypertension. It should also be noted that in the low CV risk cohort, all patients in both the group exposed to statins, ACE inhibitors, and ARBs and the reference group were exposed to NSAIDs, thereby precluding demonstration of any effect of this class on outcomes. All analyses were done using SAS version 9 (SAS Institute, Cary, North Carolina). Differences between cases and controls were assessed using *t* tests and chi-square analysis and confirmed using univariate conditional logistic regression.

RESULTS

Table 1 gives a summary of the number of cases and controls that were identified for each end point, for both the high- and low-risk cohorts, and with respect to whether steroid use was excluded or included.

Table 2 shows features for cases (n = 946) and controls (n = 18,774) for the COPD hospitalization end point identified from the cohort of patients with both COPD and

Table 2. Demographics of Cases and Controls in Chronic Obstructive Pulmonary Disease Patients Not Using Steroids in the Year Prior to Cohort Entry and Who Had Coronary Revascularization (High-Risk Cohort)

	Cases (n = 946)	Controls (n = 18,774)	p Values
Age at index date (yrs, mean ± SD)	72 ± 6	72 ± 6	0.5245
Gender (%)			
Female	35	34	0.5029
Male	65	66	
Hospitalizations in year preceding cohort entry (%)			
Prior myocardial infarction	5.9	7.3	0.1182
Congestive heart failure	3.9	2.9	0.0869
Pneumonia	3.0	1.6	0.0018
Co-variate medications in year preceding cohort entry (%)			
Calcium channel blockers	33.2	36.5	0.0383
Beta-blockers	17.1	24.0	<0.0001
Diuretics	24.7	24.7	0.9967
Nitrates	28.7	33.0	0.0053
Anti-diabetic	14.5	14.6	0.2304
Inhaled anticholinergics	1.3	1.1	0.5885
Inhaled beta$_2$-agonists	3.1	3.9	0.1840
Theophylline	0.7	1.0	0.5074
In- and out-patient doctor visits in year prior to cohort entry	20 ± 25	19 ± 22	0.1012
Number of unique drugs in year prior to cohort entry	19 ± 9	16 ± 8	<0.0001

Analysis was performed with respect to end point of hospitalization for chronic obstructive pulmonary disease.

Table 3. Demographics of Cases and Controls in Chronic Obstructive Pulmonary Disease Patients Not Using Steroids in the Year Prior to Cohort Entry and Who Were Taking Nonsteroidal Anti-Inflammatory Drugs (Low-Risk Cohort)

	Cases (n = 4,907)	Controls (n = 98,097)	p Values
Age at index date (yrs, mean ± SD)	77 ± 6	77 ± 6	0.7983
Gender (%)			
Female	51	58	
Male	49	42	<0.0001
Hospitalizations in year preceding cohort entry (%)			
Congestive heart failure	2.6	2.1	0.0060
Pneumonia	3.2	2.6	0.0138
Co-variate medications in year preceding cohort entry (%)			
Calcium channel blockers	18.0	17.3	0.1832
Beta-blockers	7.5	9.3	<0.0001
Diuretics	19.3	19.0	0.6847
Nitrates	9.1	8.5	0.1214
Anti-diabetic	6.6	6.2	0.3282
Inhaled anticholinergics	0.2	0.3	0.1813
Inhaled beta$_2$-agonists	2.1	2.0	0.7075
Theophylline	0.1	0.3	0.0233
In- and out-patient doctor visits in year prior to cohort entry	5 ± 9	5 ± 19	0.6260
Number of unique drugs in year prior to cohort entry	14 ± 7	12 ± 6	<0.0001

Analysis was performed with respect to end-point of hospitalization for chronic obstructive pulmonary disease.

revascularization (high CV risk). Similarly, Table 3 shows the characteristics of cases (n = 4,907) and controls (n = 98,097) for the same end point but identified from the cohort of patients prescribed NSAIDs (low CV risk), indicating 4,907 cases and 98,097 controls. The distribution of these covariates for cases and controls for all other outcomes studied were essentially the same.

Table 4 shows the crude unadjusted RRs for the two COPD cohorts, stratified as to whether steroid users were included or not. Figures 1 and 2 demonstrate the fully adjusted RRs. In the high-risk cohort (Fig. 1), and irrespective of whether steroid users are included or not, substantial risk reduction for hospitalization for COPD was seen with use of statin (RR 0.72, 95% confidence interval [CI] 0.56 to 0.92; p = 0.0091) and with the use of statin and ACE inhibitors or ARBs (RR 0.66, 95% CI 0.51 to 0.85; p = 0.0012); when steroid users were included, the respective results were RR 0.71, 95% CI 0.56 to 0.90 (p = 0.0038) and RR 0.69, 95% CI 0.55 to 0.88 (p = 0.0027). Risk ratios were reduced for the end point of MI by all three drug

Table 4. Unadjusted Risk Ratios and 95% Confidence Intervals in the High- and Low-Risk COPD Cohorts

	High-Risk Cohort		Low-Risk Cohort	
	Steroid Users Excluded	Steroid Users Included	Steroid Users Excluded	Steroid Users Included
Hospitalization for COPD				
ACE inhibitors	1.20 (0.95–1.52)	1.18 (0.94–1.48)	1.11 (1.02–1.20)	1.05 (0.97–1.13)
ARBs	1.51 (1.08–2.11)	1.34 (0.97–1.86)	0.96 (0.86–1.07)	0.96 (0.86–1.06)
Statin drugs	0.88 (0.69–1.12)	0.89 (0.71–1.12)	0.84 (0.76–0.93)	0.79 (0.72–0.87)
Statin and ACE inhibitor or ARB	0.96 (0.75–1.23)	1.04 (0.83–1.31)	1.07 (0.94–1.21)	0.98 (0.87–1.11)
MI				
ACE inhibitors	0.62 (0.51–0.76)	0.67 (0.55–0.81)	1.58 (1.21–2.05)	1.62 (1.26–2.09)
ARBs	0.63 (0.45–0.89)	0.69 (0.51–0.95)	1.40 (1.01–1.96)	1.40 (1.01–1.93)
Statin drugs	0.44 (0.36–0.54)	0.44 (0.36–0.54)	0.93 (0.65–1.34)	1.02 (0.73–1.43)
Statin and ACE inhibitor or ARB	0.34 (0.27–0.43)	0.35 (0.28–0.44)	2.10 (1.52–2.90)	2.00 (1.46–2.75)
Death				
ACE inhibitors	1.44 (1.14–1.81)	1.52 (1.21–1.91)	1.04 (0.92–1.18)	0.97 (0.86–1.09)
ARBs	1.03 (0.71–1.49)	1.04 (0.73–1.49)	0.75 (0.63–0.90)	0.66 (0.55–0.78)
Statin drugs	0.62 (0.48–0.79)	0.65 (0.51–0.83)	0.62 (0.51–0.74)	0.56 (0.46–0.66)
Statin and ACE inhibitor or ARB	0.68 (0.53–0.87)	0.72 (0.56–0.92)	0.58 (0.46–0.73)	0.54 (0.44–0.68)
Death or MI				
ACE inhibitors	0.94 (0.81–1.09)	0.92 (0.80–1.07)	1.11 (1.00–1.24)	1.15 (1.03–1.29)
ARBs	0.88 (0.69–1.12)	0.89 (0.71–1.11)	0.81 (0.69–0.95)	0.87 (0.75–1.01)
Statin drugs	0.53 (0.45–0.62)	0.55 (0.47–0.64)	0.69 (0.59–0.81)	0.73 (0.63–0.85)
Statin and ACE inhibitor or ARB	0.49 (0.42–0.58)	0.50 (0.42–0.58)	0.80 (0.67–0.96)	0.83 (0.69–0.99)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CHF = congestive heart failure; MI = myocardial infarction.

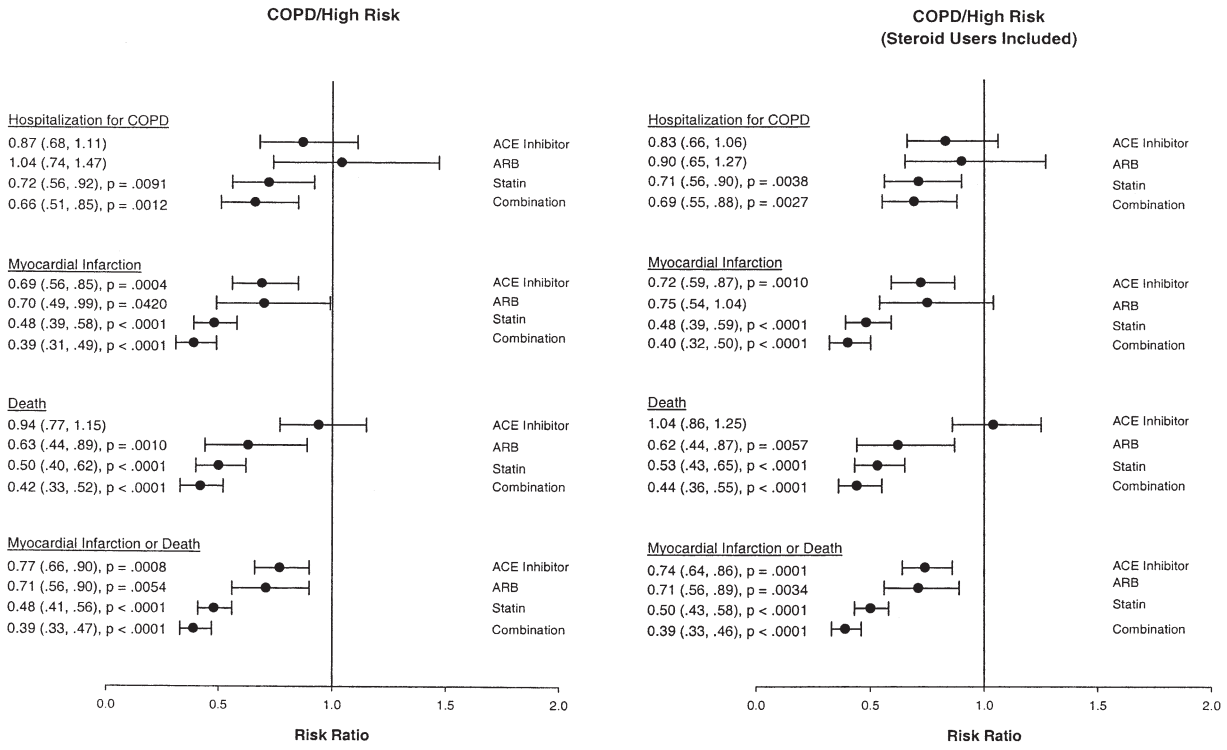

Figure 1. Fully adjusted risk ratios are plotted for the end points of hospitalization for chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), death, and MI or death. Treatments analyzed were angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), statins (hydroxymethylglutaryl CoA reductase inhibitors [HMG-CoA]), and the combination of statins with ACE inhibitors or ARBs (combination) in the population of COPD patients with prior revascularization (high risk). Results including steroid users are in the **right panel**.

classes and especially by the combination of statin with either ACE inhibitor or ARB (RR 0.39, 95% CI 0.31 to 0.49; $p < 0.0001$). Similar reductions were seen when steroid users were included in the COPD cohort, except that the risk reduction for ARBs was not significant. Death risk ratios were reduced by ARBs (RR 0.63, 95% CI 0.44 to 0.89; $p = 0.0010$), statins (RR 0.50, 95% CI 0.40 to 0.62; $p < 0.0001$), and statins with ACE inhibitors or ARBs (RR 0.42, 95% CI 0.33 to 0.52; $p < 0.0001$). Virtually identical results were seen when steroid users were included. Risk ratios for the combined end point of death or MI were significantly reduced by ACE inhibitors (RR 0.77, 95% CI 0.66 to 0.90; $p = 0.0008$), ARBs (RR 0.71, 95% CI 0.56 to 0.90; $p = 0.0054$), statins (RR 0.48, 95% CI 0.41 to 0.56; $p < 0.0001$), and the combination of statins with ACE inhibitors or ARBs (RR 0.39, 95% CI 0.33 to 0.47; $p < 0.0001$). Again, virtually identical results were seen when steroid users were included.

Figure 2 shows the key results in the low-risk group analyses. The main difference between this analysis and the analysis in the high-risk groups is a lack of benefit in prevention of MI. The only difference between the inclusion of steroid users (right panel) and their exclusion in the low-risk cohort analysis is in the efficacy of ACE inhibitors for the reduction of hospitalization for COPD. When steroid users were excluded, this result was not statistically significant, whereas when steroid users were included the results were statistically significant (RR 0.90, 95% CI 0.83 to 0.98; $p = 0.0107$).

DISCUSSION

This observational study suggests that the cardioprotective effects of statins, ACE inhibitors, and ARBs extend also to COPD patients regardless of their concomitant CV risk profile and whether steroid users are included or not in the analyses. The risk reductions ranging from 10% to 66% may possibly be due to the coexistence of COPD and coronary disease, coexistence of numerous risk factors for CV disease commonly seen in COPD patients (e.g., smoking, obesity, diabetes, hypertension), and perhaps also because of the synergy between CV events and pulmonary inflammation (29–31). In addition, and of special importance, these agents also seem to affect pulmonary disease itself, as suggested by reduced hospitalizations for COPD. This is possibly due to mitigation of pulmonary injury by statins and drugs affecting angiotensin II (12–24). The possibility that these classes of drugs have dual cardiopulmonary protective properties has not been seriously considered in discussions of new therapies for COPD (32).

The strengths of this study include the large cohorts of COPD patients with various CV risk profiles (Table 1), the fact that they are representative of the general population, the statistical control of many known confounders, including control for calendar time bias, other clinical events, and

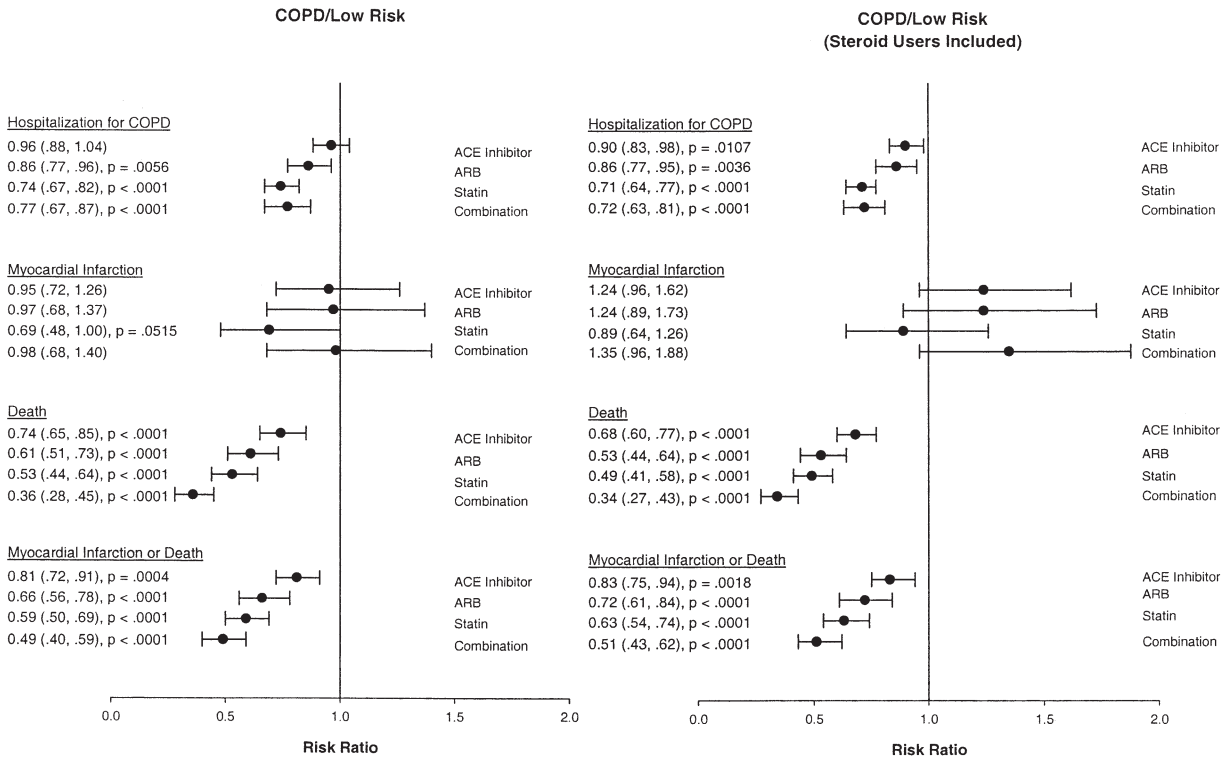

Figure 2. Fully adjusted risk ratios are plotted for the end points of hospitalization for chronic obstructive pulmonary disease (COPD), myocardial infarction (MI), death, and MI or death. Treatments analyzed were angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), statins (hydroxymethylglutaryl CoA reductase inhibitors [HMG-CoA]), and the combination of statins with ACE inhibitors or ARBs (combination) in the population of COPD patients without previous MI and newly treated with nonsteroidal anti-inflammatory drugs (low risk). Results including steroid users are in the **right panel**.

drug usage, the high frequency of events, which allows for calculation of reasonably precise estimates of risk reduction, and, perhaps most important, the relative consistency of results in the two cohorts and irrespective of whether steroid users were included or not. On the other hand, our analyses and conclusions must be considered speculative, because they are based on a retrospective cohort analysis rather than a randomized clinical trial. As such, the results may be susceptible to confounding or channeling bias. For example, the databases did not allow us to adjust for all known potential confounders, including severity of COPD, smoking, or severity of known CV risk factors such as dyslipidemia. Accordingly, these results are best seen as hypothesis generating. However, we believe that the magnitude of potential benefit provides compelling evidence to justify a randomized clinical trial, particularly given the dearth of disease-modifying therapies for the increasing prevalence of patients with COPD. Because the confidence limits of the risk reductions seen with statins and the combination of statins and ACE inhibitors or ARBs overlap, it would be particularly important to ensure sufficient power in prospective trials to determine if synergy truly exists between statins and ACE inhibitors or between statins and ARBs. It would also be important to determine if COPD patients at lower risk are truly recalcitrant to reductions in MI, an outcome that we did not anticipate, or whether this simply represents a lack of power in the present study for this outcome. Similarly, the mechanism for reduced total mortality in this lower-risk cohort requires consideration of end points other than MI or hospitalization for COPD that might explain that effect. Finally, the effects of these agents on other pulmonary events (e.g., recurrent pneumonia, deterioration of pulmonary function, and so on) and mechanisms of pulmonary injury merit further elucidation. Accordingly, we believe that these results provide strong impetus for a paradigm shift in the scientific approach to treatment of COPD and that properly controlled clinical trials are warranted to validate these important observations.

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